REMARKS

Applicants filed an Amendment and Response ("the Amendment") on December 3, 2007, in reply to the final Office Action dated October 2, 2007. In reply to Applicants' Amendment, the Patent Office issued a Notice of Non-Compliant Amendment, stating the text "increase agonist-induced down-regulation of the G protein-coupled receptor" has been deleted from Claim 18 without the appropriate markings (strikethrough). In the instant amendment, this informality has been corrected. The content of this amendment is otherwise substantially identical to that of the amendment filed December 3, 2007. It is believed that the instant amendment fully complies with the requirements under 37 C.F.R. § 1.121. Also filed concurrently is a Request for Continued Examination. Thus, Applicants respectfully request entry of this amendment and consideration of the remarks presented herein.

In the instant amendment, Claims 2-9 and 19-23 have been canceled without prejudice. Claims 1, 10, 11, 16 and 18 have been amended. Upon entry of the instant amendment, Claim 1, 10-11, 13-18, 24-25 and 27-29 will be pending and under consideration.

I. AMENDMENTS TO THE SPECIFICATION

The specification has been amended at paragraphs [0244]-[0245] at page 70 to correct typographic error as to the figure number. The specification has been further amended at paragraph [0247] at page 70 to insert a sequence identification number.

Applicant submits that these amendments do not introduce any new matter and are fully supported by the specification as originally filed. Entry and consideration of these amendments are therefore respectfully requested

II. AMENDMENTS TO THE CLAIMS

Claims 2-9, 12, 19-23 and 26 have been canceled without prejudice to Applicants' right to pursue the canceled subject matter in one or more related patent applications.

Claims 1, 10, 11, 16 and 18 have been amended. Support for the amendments to Claim 1 can be found, for example, in the specification, at paragraph [0092] at page 22, paragraph [0096] at pages 23-24. Support for the amendments to Claim 18 can be found, for example, in the specification, at paragraph [0104] at page 26, and paragraph [0107] at pages 26-27.

Applicant submits that these amendments do not introduce any new matter and are fully supported by the application as filed. Accordingly, entry and consideration of the amendments are respectfully requested.

III. CLAIM REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-11, 13-25 and 27-29 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly as failing to comply with the enablement requirement. Claims 2-9, 12, 19-23 and 26 have been canceled and the rejection is moot in view of their cancellation.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. Manual of Patent Examining Procedure (hereafter "MPEP") § 2164.04, (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, "[a] specification disclosure...must be taken as being in compliance with the enablement requirement ...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* (emphasis added).

The Patent Office alleges that the specification is not enabling because it fails to describe an inhibitor that reduces the interaction between a G protein-coupled receptor associated sorting protein 1 ("GASP1") polypeptide and a G protein-coupled receptor ("GPCR"). *See* the Office Action, pages 2-3. Although Applicants do not agree with the Patent Office's allegation, to advance the prosecution of the instant application, Applicants have amended Claims 1, 10, 11, 16 and 18. Claim 1 has been amended to recite a method of inhibiting agonist-induced down-regulation of a GPCR comprising contacting cells comprising the GPCR with a GASP1 polypeptide comprising the amino acid sequence of SEQ ID NO: 8 in an amount sufficient to reduce agonist-induced down-regulation of the GPCR in the cell. Claims 10-11 and 13-17 depend from Claim 1. Claim 18 has been amended to recite a method of enhancing agonist-induced down-regulation of a GPCR comprising contacting cells comprising the GPCR with a GASP1 polypeptide comprising the amino acid sequence of SEQ ID NO:2 in an amount sufficient to increase agonist-induced down-regulation of the GPCR. Claims 24-25 and 27-29 depend from Claim 18. These claims are examined to the extent that they are for *in vivo* use according to the Restriction Requirement dated June 19, 2007.

Applicants respectfully submit that Claims 11, 10-11, 13-18, 24-25 and 27-29 as amended are enabled because no undue experimentation is required for those of skill in the art to make or use the claimed invention based on the disclosure in the present application, coupled with information known in the art. The specification provides sufficient guidance for how to make and use the claimed invention. For example, the specification provides the sequence of GASP1 polypeptides. *See* the specification, page 28, paragraph [0113]. The specification further teaches how to make and produce the GASP1 polypeptides by synthetic or recombinant techniques. *See* the specification, pages 34-35, paragraphs [0122]-[0129]. The specification teaches that GASP1 polypeptides can bind the cytoplasmic tail of delta opioid receptor ("DOR") *in vivo*. *See* the specification, pages 69-71, paragraphs [0244]-[0246]; Figures 2-3. The specification further provides data to show the function of GASP1 polypeptides in mediating sorting of DOR to lysosomes. *See* the specification, pages 71-73, paragraphs [0248]-[0250]. As measured by radioligand binding, agonist-induced down regulation of DOR was significantly enhanced both in rate and in extent in cells overexpressing GASP 1 polypeptides comprising the sequence of SEQ ID NO:2. *See* the specification, pages 72-73, paragraph [0250], Figure 4(F). Agonist-induced down regulation of DOR was significantly inhibited in cells overexpressing GASP 1 polypeptides comprising the sequence of SEQ ID NO:8. *See* the specification, pages 71-72, paragraphs [0249]-[0250], Figure 4(E). The specification then confirms that this GASP sorting function is general to a larger class of GPCRs by showing that GASP 1 polypeptides can bind the cytoplasmic tail of numerous GPCRs such as dopamine D4 receptor, B2AR *etc.* *See* the specification, pages 73-74, paragraphs [0251]-[0252], Figure 5. Therefore, based on the teachings in the specification, it is clear that a sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention. Accordingly, Applicants respectfully submit that no undue experimentation is required for make or use Claims 1, 10-11, 13-18, 24-25 and 27-29, and that these claims are fully enabled by the specification

The Patent Office alleges that the claimed invention is not enabled because the application does not provide a single *in vivo* working example of the claimed methods Applicants respectfully disagree.

Applicants respectfully remind the Patent Office that a rigorous or an invariable exact correlation between *in vitro* or *in vivo* animal model assays and a claimed method of use is not required. *See Cross v. Iizuka*, 224, U.S.P.Q. 739, 747 (Fed. Cir. 1985). The test is

whether those of skill in the art would accept the test as reasonably correlating to the claimed method. *See In re Brana* 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). In addition, since the initial burden is on the Patent Office to give reasons for the lack of enablement, the Patent Office must give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. *See Cross v. Iizuka*, 224, U.S.P.Q. 739, 747 (Fed. Cir. 1985).

The specification discloses data to show that GASP 1 polypeptides can modulate agonist-induced down regulation of PCR by regulating endocytosis of GPCRs in cell lines overexpressing GASP 1 polypeptides. *See* the specification, Example 1. It was known in the art that peptides that are capable of regulating endocytosis of GPCRs *in vitro*, such as enkephalin, can also regulate endocyotosis of GPCRs *in vivo*. *See* He *et al.*, 2002, *Cell* 108(2):271-282, a copy of which is submitted with IDS filed herein. Therefore, those of skill in the art would accept *in vitro* assays showing the ability of GASP 1 polypeptides to modulate agonist-induced down regulation of GPCRs as reasonable correlating with *in vivo* use of GASP 1 polypeptides as recited by Claims 1-11, 13-25 and 27-29.

Accordingly, it is respectfully requested that the rejection Claims 1-11, 13-25 and 27-29 under 35 U.S.C. § 112, first paragraph, be withdrawn.

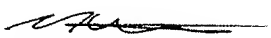
CONCLUSIONS

In light of the above amendments and remarks, the Applicants respectfully request that the Patent Office reconsider this application with a view towards allowance.

The Commissioner is hereby authorized to charge any required fee to Jones Day Deposit Account No. 50-3013 (order no. 405435-999011).

Respectfully submitted,

Date: March 28, 2008



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